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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,716	02/05/2004	Jeffrey A. Whitsett	10872.0517745	5622

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FROST BROWN TODD, LLC
2200 PNC CENTER
201 E. FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@fbtlaw.com
rgaunce@fbtlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/772,716	WHITSETT, JEFFREY A.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007 and 29 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *3,5-16 and 25-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-43* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 4, and 18-24 are under consideration as drawn to FoxA2 protein, treatment of acute inflammatory lung disease.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicants have indicated that they would like a suggestion as to how the title should be amended. It is suggested that reference to FoxA2 as the active agent be included in the title.

Claim Interpretation

It is noted that FoxA2 is also known in the art as HNF-1 beta, HNF3 beta, and forkhead 2.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4 and 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 as amended is indefinite as the metes and bounds of the terms "substantially homologous and "native" cannot be determined. With regard to the former term, the specification defines such as:

Claim 1 is indefinite because

[0033]The term "substantially homologous" refers to sequences that are at least 90%, more preferably at least 95% identical, more preferably at least 97% identical, or more preferably at

least 99% identical. Homologous sequences can be the same functional gene in different species.

It is not clear whether or not "the same functional gene in different species" must meet the 90% requirement as well. With regard to the term "native", the term has two accepted meanings in the art; non-dentured, or naturally occurring. The specification breathes no life and meaning into the term. With respect to the latter possibility, since all native FoxA2 have not been discovered or described, if that definition is what is intended, it is impossible to determine the metes and bounds of such.

Claim 19 as amended renders both itself and claim 1 indefinite; the claim states that the FoxA2 therapeutic agent decreases lung inflammation; it is not clear that this constitutes a further method step, because if it did, then it is not clear what the "therapeutically effective amount" of claim 1 is, since claim 1 clearly indicates that the condition being treated is inflammatory lung disease.

The remaining claims are rejected for depending from a rejected claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 21 as amended indicates that an additional anti-inflammatory agent is administered that is "effective for reducing eosinophilic inflammation." Neither that phrase nor even the term eosinophil occurs in the specification.

Claims 1, 2, 4 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention, as claimed, is a method of treating pulmonary disease by administering to the airway of a mammal FoxA2 protein. A number of diseases are specifically listed, see for example claims 18 and 24. Additionally, claim 19 states that the administration results in decreased lung inflammation. Even though the claims are now limited to FoxA2 protein, the specification defines such at page 27 as including "peptides, oligopeptides, and proteins, including modifications thereof, including amino acid variants and "other modifications", with no requirement for structural identity or conservation as compared to any disclosed particular protein. Thus the breadth of the claims includes treatment of any pulmonary disease by administration of any "FoxA2 therapeutic".

The specification provides in the way of guidance that deletion of FoxA2 impairs lung morphogenesis (page 85) as is associated with goblet cell hyperplasia in mice (page 85-86), that FoxA2 is reduced in mouse models of goblet hyperplasia (page 88), that "KC", or keratinocyte-derived cytokine, was found to be increased in FoxA2 deleted mice, but no other cytokine was so identified, including IL-4,5,6,9, 10, 11, 13, 17, and TNFα (page 89). It is disclosed that FoxA2 inhibits transcription of the MUC5A/C gene in vitro, which gene is associated with goblet cell phenotype (page 89), but no other goblet cell phenotype-associated genes. It is also disclosed that FoxA2 is decreased in lung tissue from four adults with cystic fibrosis, one with chronic pulmonary infection and bronchiectasis, and five infants with bronchopulmonary displasia (pages 89-90). Deletion of FoxA2 from a transgenic animal, or observation that FoxA2 is missing in a patient is not predictive of the effect of administering FoxA2 protein.

There is no causality established between the reduction in FoxA2 and any disease or condition. There are no working examples in which FoxA2 protein was administered *in vitro* or *in vivo*, nor what the effect of such administration might be.

The level of predictability in the art is low. It is not recognized by the art the gene deletion experiments or the detection of decreased protein level, as disclosed in the specification

is predictive of success in treatment. Even if such were predictive, the claims are broadly drawn to all pulmonary disease, and all "FoxA2", which are broad (and in the latter case, indefinite) categories.

The FoxA2 protein is known in the art to be a transcriptional activating protein. This means that it acts within the nucleus of the cell. It is not predictable that merely administering the protein extracellularly would result in internalization of the protein in active form, nor that the protein would reach the nucleus, its site of action. As the claims are specifically drawn to treatment of the airway, there are further complicating factors; the presence of bacteria (which make proteases) and mucus, which make it further unpredictable that the protein would be able to penetrate the cells in active form. The specification provides neither guidance nor working examples of such.

The art recognizes that FoxA2 is a transcription factor. For example, Nishizaki et al. (Mech. Dev. 102 :57, 2001) teach that FoxA2 is a transcription factor that is essential for development of the node and notochord (abstract), and that it is highly conserved across species; see figure 1.

FoxA2 was recognized in the art as being involved in transcriptional control in lung epithelium. However, as taught by Weidenfeld et al. (JBC 277:21061), using WNT7b promoter, such gene expression is complex, and due to a combination of transcription factors, including (in the case of WNT7b) TTF-1 and GATA6. Thus, the effect of administration of FoxA2, even if the protein were properly internalized in active form, would not be predictable.

Wang et al. (JBC 20 :17564, 2002) teach that FoxA2 controls multiple genes implicated in metabolism-secretion coupling of glucose-induced insulin release (title). They further teach that overexpression of FoxA2 results in blunted glucose stimulated insulin secretion (abstract). At page 21069, second column, they disclose that FoxA2 had been shown to regulate several lung-specific genes, including SP-A, SP-B, CC10, and WNT7b. They state that the WNT7b promoter may be regulated in a "complex and possibly redundant manner by members of the Fox gene family". The art does not correlate the expression of SP-A, SP-B, CC10, and WNT7b to any specific disease states. Further, if the regulation of such genes is "complex and possibly redundant", the effect of administering FoxA2 protein would be entirely unpredictable. With respect to WNT7b, US Publication 20040023259 discloses that the expression of WNT7b is

regulated by transcription factors including TTF-1, GATA6 and FoxA2; thus, FoxA2 is not the only point of regulation of that gene.

FoxA2 expression is not limited to early development, nor to pulmonary tissues. For example, Lehner et al. (FASEB J 21:1445, 2007) disclose that FoxA2 is specifically induced in colorectal liver metastases. Lee et al. (Diabetes 51 :2546, 2002) teach that FoxA2 controls Pdx1 gene expression in pancreatic beta cells in vivo. Rausa et al. (MCB 23 :437, 2003) disclose that upregulation of FoxA2 in liver caused diminished hepatocyte glycogen levels and reduced expression of glucose homeostasis genes(abstract). They further teach that "depending on the target sequence, FoxA2 and HNF-6 protein interaction can either synergistically stimulate or repress transcription." Foucher et al. disclose joint regulation of the MAP1B promoter by FoxA2 and Engrailed. Finally, Ceelie et al. (J. Thrombosis and Haemostasis 1:1688) teach regulation of prothombin gene expression by FoxA2 and four other transcription regulatory proteins. Finally, US Publication 20050266438 discloses at paragraph [0160] that "overexpression of Foxa2 is associated with steatosis and mitochondrial damage" see also Hughes et al., Hepatology 37:1414. Thus, the effect of administering FoxA2 could be extremely detrimental, and would require significant research to determine how and in what amount it could be safely administered, assuming that the protein could be successfully administered at all.

In view of the fact that it is not recognized in the art to administer FoxA2 as a protein, nor is it predictable that it would be internalized via the lung epithelium, FoxA2 is a transcription factor that interacts with numerous other homeobox transcription factors, and my increase or decrease gene expression depending upon the gene, the cell, and the presence of other transcription factors, there is no pulmonary disease that has been shown to have a causal relationship with FoxA2 protein levels such that supplying the protein would be expected to have a beneficial effect and finally that the art recognizes that FoxA2 gene regulation is complex, widely spread, occurring at least in developmental gene regulation, glucose homeostasis, glycogen expression, and prothombin, it would require undue experimentation to determine what conditions, if any, could be treated by administration of FoxA2 protein, and how they could be so treated. Accordingly, applicants have not disclosed to one of ordinary skill in the art how to use the protein as a pharmaceutical or therapeutic agent. There is an insufficient written description of the invention with respect to the in vivo operability of the protein to enable one of ordinary skill in the art to use applicants' invention. Furthermore, applicant has provided no

teaching or guidance indicating what dosages are required and what way(s) the protein can be administered (see Ex parte Powers, 220 U.S.P.Q. 924 (Bd. Pat. App. & Int. 1982)) or otherwise used in a practical manner. It would, therefore, require undue experimentation of one of ordinary skill in the art to determine how to use the methods. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Apprlicants traversal of theis rejection, filed 12/3/2007, has been fully considered but its not deemed persuasive.

At page 11 of the response, applicants allege that it is "well established n the art that such proteins can be administered...." However, applicants refer to no such are in support of their allegation, nor is the information stated in the argument found in the specification.

At page 12, appliants argue that the examiner "has not provided sufficient evidence" to support the rejection for lack of enablement. Applicants argument has been fully considered but is not deemed persuasive. The Examiner provided sound scientific reasoning, supported by numerous publications in the art supporting her position. As the USPTO does not possess laboratory facilities, the Examiner cannot herself prove the lack of enablement via clinical studies.

It is believed that all pertinent arguments have been addressed. Accordingly, the rejection is maintained for reasons cited above.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
Primary Examiner
Art Unit 1647